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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,333	KHVOROVA ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 19-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 19-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Sequence Information

1. On page 2 of the response filed 10/25/05 Applicants requested the insertion of the paper copy of the sequence listing submitted on CD-ROM in lieu of paper, into the specification after page 159 but before page 160. However, there is no request to remove the pages corresponding to the previous sequence listing, submitted on 06/30/2004, that was inserted into the specification after page 159 and before page 160.

Response to Arguments

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Those rejections set forth in the prior Office Action, but not repeated in the instant Office Action have been withdrawn in response to Applicant's amendment and/or arguments.

Claim Rejections - 35 USC § 112

4. Claims 2-5 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2, and those claims dependent therefrom, claims 3-5, recite the phrase "applying at least on of Formulas I, II and IV-IX to said at least one candidate siRNA, wherein Formulas I-IX are," however the claims have been amended to remove formula III, therefore the limitation of "Formulas I-IX" is improper since the limitation encompasses formula III. Additionally, claims 2 and 19 recite wherein $Tm_{20}{}^{\circ}C = 1$ if the

Tm is greater than 20°C, however there is no numerical value given in the claim for wherein $Tm_{20}{}^{\circ}C$ is less than or equal to 20°C. Claim 2 also recites the following phrase multiple times "the sense strand is only 18 base pairs in length." This phrase is inconsistent with the limitation in claim 1 which recites that the "rationally designed siRNA comprises 19-25 nucleoside base pairs," therefore it is unclear how the sense strand can be 18 base pairs in length at any point.

5. Claims 1-6, 8, 19-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The instant claims have been amended to recite "[A] method for selecting a rationally designed siRNA, wherein said rationally designed siRNA comprise..." According to Applicant's response, on page 26, 1st paragraph, "the phrase 'rational design' is defined as increasing the probability that an siRNA will be functional." The phrase "rational design" is not limited to the definition provided in Applicant's response. Contrary to Applicant's assertions, the specification as filed states, on page 21, lines 23-27, that "rational design can be described in a variety of ways. Rational design, in its simplest terms, is the application of a proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA." It is noted that the definition of "rational design," is not so limited in the instant claims as suggested by Applicant's arguments. As per MPEP § 2106[R-3]II.C. "Office personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). Limitations appearing in the specification but not recited in the claim are not read into the claim. E-Pass Techs., Inc. v. 3Com Corp., 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir.

2003) (claims must be interpreted "in view of the specification" without importing limitations from the specification into the claims unnecessarily)."

If Applicant's intend that the phrase "rational design," is to be limited to "the application of a proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA," the claims should be amended to recite this definition, since the specification as filed clearly contemplates wherein the phrase "rational design," can be described in a variety of ways..." (see page 21, line 23 of the specification as filed).

The instant claims are drawn broadly to a method for selecting rationally designed siRNA comprising selecting a target gene, and applying at least one non-target specific criterion to a least one candidate siRNA sequence. The claimed methods require the applying of at least one "non-target specific criterion," and selecting a rationally designed siRNA from said at least one candidate siRNA. However, the methods do not recite a step wherein the results produced from the application of the "non-target specific criterion" to said at least one candidate siRNA, is correlated with the "rationally designed" siRNA.

Although claim 2 recites formulas to further limit part (b) of the method of claim 1, the claims do not recite the particular desired values for the outcomes of applying the formulas recited in the instant claims, such that a determination of the relative functionality of the candidate siRNA can be evaluated based upon the non-target specific criterion. As stated in the specification as filed, bridging paragraph for pages 25-26, formulas I-VII provide ***relative*** information regarding functionality. This statement

suggests the necessity of a comparison between two distinct candidate siRNA molecules. The instant claims do not recite the need for any comparative step. The specification at pages 25-26 further recite: "When the values for two sequences are compared for a given formula, the relative functionality is ascertained; a higher positive number indicates a greater functionality. For example, ***in many applications*** a value of 5 or greater is beneficial." However, there is no specific information given regarding what particular ***applications*** are referred to in this instance. Knowledge of the particular ***proven set of criteria***, appears to be critical to the practical application of the instant claims, wherein said method allows the *rational design* of an siRNA molecule, otherwise the application of the formulas recited in, for example claims 2 and 19, does not provide you with any guidance regarding how to evaluate the numerical value produced from the given formulas.

Since formulas I-IX are formulas for ascertaining "relative functionality," the claims are incomplete since the claims do not recite a step wherein the values produced from the application of formulas I-IX to one candidate siRNA are compared with the values produced from another candidate siRNA, or compared to a standard value, such that the relative functionality with respect to the other candidate siRNA or with respect to a standard can be determined.

However, even formulas I-IX do not appear to be a ***proven set of criteria*** since Applicant's own specification describes the limitations associated with the application of the various formulas recited in the claims, in particular at page 26, lines 4-29:

> Additionally, in many applications, more than one of these formulas would provide useful information as to the relative functionality of potential siRNA sequences. However, it is beneficial to have more than one type of formula, because not every formula will be able to help to differentiate among potential siRNA sequences. For example, in particularly high GC mRNAs, formulas that take that parameter into account would not be useful and application of formulas that lack GC elements (*e.g.*, formulas V and VI) might provide greater insights into duplex functionality. Similarly, formula II might by used in situations where hairpin structures are not observed in duplexes, and formula IV might be applicable for sequences that have higher AU content. Thus, one may consider a particular sequence in light of more than one or even all of these algorithms to obtain the best differentiation among sequences. In some instances, application of a given algorithim may identify an unususally large number of potential siRNA sequences, and in those cases, it may be appropriate to re-analyze that sequence with a second algorithm that is, for instance, more stringent. Alternatively, it is conceivable that analysis of a sequence with a given formula yields no acceptable siRNA sequences (*i.e.* low SMARTscores™). In this instance, it may be appropriate to re-analyze that sequences with a second algorithm that is, for instance, less stringent. In still other instances, analysis of a single sequence with two separate formulas may give rise to conflicting results (*i.e.* one formula generates a set of siRNA with high SMARTscores™ while the other formula identifies a set of siRNA with low SMARTscores™). In these instances, it may be necessary to determine which weighted factor(s) (*e.g.* GC content) are contributing to the discrepancy and assessing the sequence to decide whether these factors should or should not be included. Alternatively, the sequence could be analyzed by a third, fourth, or fifth algorithm to identify a set of rationally designed siRNA.

Although the specification describes a variety of non-target specific criteria, see criteria 1-11 on pages 21-22, to evaluate, as per the above passage, it does not appear that these criteria represent ***a proven set of criteria*** as required for the rational design of an siRNA, since the application of one or more of these criteria may or may not give

you the desired result, or even give you conflicting results, and re-analysis with another algorithm may be required, or furthermore re-analysis with a third, fourth, or fifth algorithm may be required to identify a set of rationally designed siRNA.

Additionally, in the bridging paragraph of pages 40-41, Applicants state the following: "[I]n an effort to improve selection further, all identified criteria, ***including but not limited to those listed in Table IV*** were combined into the algorithms embodied in Formula VIII and Formula IX. Each siRNA was then assigned a score (referred to as a SMARTSCORE™) according to the values derived from the formulas. Duplexes that scored higher than 0 or 20, for Formulas VIII and IX, respectively, effectively selected a set of functional siRNAs and excluded all non-functional siRNA. Conversely, all duplexes scoring lower than 0 and 20 according to formulas VIII and IX, respectively, contained some functional siRNAs but included all non-functional siRNAs." Applicant's specification (as described above, noting the highlighted text) appears to suggest the presence of certain undefined criteria embedded within the formulas according to Formulas VIII and IX, that are useful for evaluating functionality beyond those described in Table IV, however due to the multiple permutations associated with these formulas, the skilled artisan is left to guess as to which parameter is the most essential parameter for assessing functionality.

Moreover, Applicant's guidance for specifically choosing functional siRNA based upon the use of the SMARTSCORE™ (i.e. Formulas VIII and IX, as stated above) siRNA ranking is confusing since, at page 53, the specification teaches that in order to identify hyperfunctional siRNA (i.e. siRNA that induce greater than 95% silencing of a

specific target when transfected at subnanomolar concentrations, see page 14, lines 28-30) siRNA with a superior SMARTSCORE™ of > -10 are selected. This statement conflicts with the statement on pages 40-41, wherein it was stated that siRNAs that scored higher than 0 or 20 for Formulas VIII and IX, respectively, effectively selected a set of functional siRNAs and excluded all non-functional siRNA, however those with a lower score included ***all non-functional siRNAs,*** and contained ***some*** functional siRNAs. It is clear that the scope of the phrase "SMARTSCORE™ of > than –10," encompasses scores that are lower than both 0 and 20 with respect to formulas VIII and IX.

These conflicting passages renders the specification as filed confusing since the skilled artisan is not given any specific guidance for rationally designing the functional siRNAs according to the present invention.

Moreover, Applicant's claims recites applying at least one non-target specific criterion to at least one candidate, in regards to formulas VIII and IX it is clear that these formulas involves the consideration of target specific criteria, particularly in regards to the presence or absence of inverted repeats in the target site, the presence of the inverted repeat yields a value of 100 for Tm, however the absence of the inverted repeat yields a Tm value of 0. The differences in the values of Tm are so significant that the presence or absence of an inverted repeat sequence in the target sequence can have a drastic effect on the outcome of the values produced from the applying of Formula VIII or IX. This observation suggests that the claimed invention cannot be practiced with merely the consideration of non-target specific criterion, as suggested by

Applicant's. Additionally, the use of the phrase "sense strand," in the recited claims, is not limited to the sense strand of the respective candidate siRNA, this phrase can also encompass the target site sense strand.

Due to the lack of clear guidance set forth in the specification as filed that for selecting functional and hyperfunctional siRNA according to the present invention, the skilled artisan would not have been able to practice the full scope of the claimed invention without undue experimentation since the skilled artisan would have to resort to unpredictable *de novo* experimentation without particular guidance from the specification as filed. There are a variety of suggestions given regarding the evaluation of particular non-target specific criterion, however the skilled artisan is not given clear and specific guidance as how to use these particular criteria for rationally designing a functional or hyperfunctional siRNA. Moreover, apart from further experimentation, without particular guidance from the specification as filed, there is no clear guidance for the selecting the particular criteria necessary for the rational design of siRNA.

Additionally, instant claims 3-5 recite a method of gene silencing comprising selecting said rationally designed siRNA according to claim 2 and introducing said rationally designed siRNA into a cell. The instant claims encompass gene silencing *in vivo* for the therapeutic treatment of a disease, see for example page 34, lines 11-14, which states that useful applications include, but are not limited to gene therapy and therapeutics. However, the prior art teaches that there is significant unpredictability associated with attenuating expression of a target gene in all types of cells, including mammalian cells, by RNA interference (RNAi). While it is recognized that introduction of

dsRNA that is targeted to a specific gene may result in attenuation of expression of the targeted gene, the degree of attenuation and the length of time that attenuation is achieved is not predictable. Caplen et al. (Gene 2000, vol. 252, p.95-105) provide evidence of the unpredictability of dsRNA attenuation of a targeted gene in vertebrate cells *in vitro*. Caplen et al. report that although dsRNA inhibits gene expression in cultured *Drosophila* cells, screening of three commonly used cell lines from three different species: human, hamster, and mouse, using cells expressing transgenes both transiently and permanently, produced mixed results.

RNA interference is recognized in the art as not enabled for therapeutic purposes. Caplen (2003) points out that, even post filing in 2003, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (see page 581) Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes that therapeutic methods are not yet effective. Thus, the post-filing art clearly suggests that administering dsRNA, either *in vitro* or *in vivo*, to attenuate expression of target genes is not a reproducible or predictable art.

The specification as filed does not provide any particular guidance and/or instruction that would enable the skilled artisan to overcome the known unpredictability

associated with the therapeutic use of dsRNA, such that the skilled artisan would be able to practice the full scope of the claimed invention without undue experimentation.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 19 remains rejected for the reasons of record, and claims 1-6, 8, and 21-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

Applicant's arguments have been fully considered, but are not persuasive. Applicants traversed the instant rejection on the grounds that the examiner has not met the burden of presenting a *prima facie* case of lack of written description, and has not presented sufficient evidence or provided sufficient reasons as to why a person of ordinary skill in the art would not recognize in the disclosure of a kit as claimed. Moreover, Applicants argue that the formulas recited in the claims describe structural limitations, not functional limitations that exist independent of structure. Applicants argue that the decision of *Pfaff v. Wells Electronics, Inc. (1999)* decision, particularly wherein it was determined that "[A]n invention need only be described with 'sufficient clearness and precision to enable those skilled in the matter to produce [it],'" supports their position. Moreover, Applicants argue that the specification discloses well over a

million sequences elected by applying Formula VIII, and almost two thousand examples are provided in Tables VI-X, and that no guesswork is required by a person of ordinary skill in the art, and that no further experimentation is required to arrive at the claimed kit. Contrary to Applicant's assertions, the scope of the instant claims encompasses siRNA to targets not disclosed in the specification as filed, and undiscovered targets, such that further experimentation would be required to optimize two separate siRNA molecules for the undiscovered target genes, their polymorphic and allelic variants of the target gene, as well as splice variants of the target gene. Unless, Applicants has evidence that they are in possession of optimized siRNA for any and all target genes, known and unknown, further experimentation would be required to optimize two siRNAs for the full scope of the target genes encompassed by the instant claims. Although, Applicants have provided a laundry list of optimized siRNAs, the manner in which Applicant's have arrived at these optimized siRNAs appears to be rather nebulous. As stated in the above rejection, the guidance in the specification is rather confusing, the instant claims, do not provide any particular guidance as to what particular values produced from the recited formulas would produce an optimized siRNA. The formulas recited in the instant claims can be used to arrive a specific value, however there is no limitation in the claims that would suggest to the ordinary skilled artisan to use these values to distinguish a suboptimal siRNA from an optimized siRNA. The teachings in the specification (pages 40-41) as filed states that siRNA with values that are 0 or 20 using formulas VIII or IX will produce functional siRNA and exclude non-functional siRNA, and siRNA with values of less than 0 and 20 will include all non-functional siRNA, however the specification

also states that siRNA with a SMARTSCORE™ of greater than –10, with includes values less than 0 and 20, can be used to identify hyperfunctional siRNA.

As stated previously, MPEP § 2163, states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." Applicant has not provided sufficient evidence to suggest that the disclosed optimized siRNA can be used to target any gene sequence, known or unknown, including all polymorphic and allelic variants of the target gene sequence, or that the disclosed optimized siRNAs can be used to predict the structures of the full scope of optimized siRNAs encompassed by the claimed invention.

Additionally, claim 1, and all claims dependent therefrom requires the application of "non-target specific criterion," and the phrase "rationally designed," requires "the application of a proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA." Applicant's have described a variety of criteria in the specification as filed, however Applicant's own specification as pages 21-22 appear to suggest that the application of these criteria may or may not be useful for identifying functional siRNA. Therefore, it is unclear if the criteria listed on pages 21-22 can be considered "a proven set of criteria that enhance the probability of identifying functional or hyperfunctional siRNA." Moreover, the instant claims encompass "non-target specific criteria," that has yet to be discovered, that are not specifically described in the specification as filed. Again, Applicant's own specification suggests that other criteria,

not specifically disclosed are encompassed within the scope of the invention, for example at page 40, criteria I-VIII are described, however at lines 27-29, it states that "in an effort to improve selection further, all identified criteria, ***including but not limited to those listed in Table IV*** were combined into algorithms embodied in Formula VIII, and Formula IX." There are so many permutations to these formulas, it is unclear what other specific proven criteria Applicants are referring to, again, apart from further experimentation the skilled artisan would not be able to specifically pinpoint the particular parameter in these formulas that would be particularly useful for identifying the full scope of functional siRNA encompassed by the claims.

The instant claims are rejected for the reasons of record, and furthermore the instant claims are considered to lack a sufficient written description regarding the application of a "proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA." Due to the ambiguity associated with the disclosure (see pages 26, 40-41 and 53) regarding which particular criteria would yield the rationally designed siRNA according to the present invention, and the apparent need for further experimentation to identify the full scope of non-target specific criteria encompassed by the instant claims, it does not appear that Applicant's were in possession of the full scope of the invention at the time of the instant invention.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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JLE